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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,063	01/15/2002	Josef Altenbuchner	21123/284981	2951

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,063	ALTENBUCHNER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/285,055.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-15-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 9-15 are currently pending in this application.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/285,055, filed on 4-2-1999.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

The disclosure is objected to because of the following informalities: a) Applicants need to update the relationship of the instant application to the parent application by noting that the parent application has matured into a US patent; b)Applicants fail to provide a specific figure description for figure 1 and 2. Appropriate correction is required.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is

particularly noted that applicants fail to provide SEQ ID NO for sequences recited in pages 12 and 15. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 and claims 10-15 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 depends from claim 1 that has been cancelled and therefore the metes and bounds of claim 9 is not clear to the Examiner. Correction is required.

Claim 9 and claims 10-15 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 and claims 10-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: identification of the specific substrates and contacting the enzyme with the substrates under appropriate conditions such that the required products are produced.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 12 is drawn to method according to claim 11, herein the hydantoins used are constantly racemized by enzymatic or chemical methods. It is not clear what enzymes are encompassed in such a method and what specific chemical methods are encompassed by the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing L-amino acids such as L-tryptophan, L-phenylalanine, and L-tyrosine by using the specific L-N-carbamoylase isolated from *Arthrobacter aurescens* having an amino acid sequence SEQ ID NO:2, encoded by the polynucleotide with SEQ ID NO:1, does not reasonably provide enablement for a method of producing any or all L-amino acids, using any carbamoylase enzyme from any source including variants mutants and recombinants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 9-15 are so broad as to encompass a method of producing any or L-amino acids using any carbamoylase enzyme from any source including variants mutants and recombinants of SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of producing any or all L-amino acids and with regard to extremely large number of carbamoylases broadly encompassed for use by the claims. With respect to the method of producing L-amino acids, the specification teaches that the substrate spectrum and the stereospecificity of the isolated rec-L-N-carbamoylase isolated from *A.aurescens* comprises of only few leading to the production of only 3 L-amino acids from a total of 20 naturally occurring L-amino acids. The specification does not teach a single universal method for producing any or all L-amino acids.

Furthermore, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the use of only the nucleotide and encoded amino acid sequence of a single carbamoylase isolated from a single source. It would require undue experimentation of the skilled artisan to first of all isolate and characterize the enzyme from any or all sources as well as to make all the polypeptides encompassed in the claims for use in the claimed method. The

specification is limited to teaching the use of SEQ ID NO:2 as a carbamoylase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications or multiple sources, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass carbamoylases from any or all sources as well as all variants and mutants of the amino acid sequence SEQ ID NOS:2 because the specification does not establish: (A) a universal method to identify the source of the above enzyme; (B)a universal method for isolation and characterization of the above enzyme from any or all sources; (C) a single universal method to produce any or all L-amino acids using the above enzyme; (D)regions of the enzyme structure which may be

modified without affecting its activity; (E) the general tolerance of carbamoylases to modification and extent of such tolerance; (F) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method f making any or all L-amino acids, and the use of carbamoylases with an enormous number of amino acid modifications to SEQ ID NOS:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the enzymes for use in the above claimed method having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for a method of producing any or all L-amino acids, wherein the N-carbamoyl amino acids are produced with hydantoinases from corresponding hydantoins and wherein the hydantoins are constantly racemized by enzymes or chemical methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 11-15 are rejected as non-enabled because applicants include a step of production of carbamoyl amino acids using hydantoins and the enzyme hydantoinase and wherein the hydantoins are constantly racemized by another enzyme or by a chemical method. Applicants fail to provide the hydantoinase enzyme and the enzyme required for constant racemization or the specific chemical method that can be used for constant racemization. Without the above enzymes, those skilled in the art would be unable to make L-amino acids using just the carbamoylase enzyme which indeed appears to require carbamoyl amino acids as its substrate.

It would require undue experimentation of the skilled artisan to first of all isolate and characterize the enzyme from any or all sources as well as to make all the polypeptides encompassed in the claims for use in the claimed method. The specification is limited to teaching the use of SEQ ID NO:2 as a carbamoylase but provides no guidance with regard to the hydantoinases and the racemases required for practicing the above method. In view of any guidance, amount of experimentation required to make the polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-

892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications or multiple sources, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the enzymes for use in the above claimed method having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9-15 are directed to the use of a genus of carbamoylase polypeptides corresponding to SEQ ID NO:2 and variants and mutants of SEQ ID NO:2. Claims 9-15 are rejected under this section of 35 USC 112 because the claims are directed to the use of a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 and fragments of SEQ ID NO:2 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the genus of modified polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences that can be derived from SEQ ID NO:2, including fragments and variants within the scope of the genus. The genus of polypeptides required for use in the claimed method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the genus for use in the claimed method which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 is directed to a method of using the enzyme hydantoinase including variants, mutants and recombinants. Claim 11 is rejected under this section of 35 USC 112 because the claim is directed to the use of a genus of polypeptides --including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue-- that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences to be used in the method encompassed by the claim. No information, beyond the characterization of the function as hydantoinase has been provided by applicants which would indicate that they had possession of the genus of polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences, including fragments and variants within the scope of the genus for use in the claimed method. The genus of polypeptides is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses not even a single a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 12 is directed to a method of using an enzyme for constant racemization in the claimed method, including variants, mutants and recombinants of said enzyme. Claim 12 is rejected under this section of 35 USC 112 because the claim is directed to the use of a genus of polypeptides --including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue-- that have not been disclosed in the specification. No description has been provided of the even a representative number of polypeptide sequences to be used in the method encompassed by the claim. No information, beyond the characterization of the function as "constant racemization" has been provided by applicants which would indicate that they had possession of the genus of polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences, including fragments and variants within the scope of the genus for use in the claimed method. The genus of polypeptides is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses not even a single a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one

skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by either Wagner et al. (US 5,516,660, 5-14-1996, cited in the IDS) or Gross et al. (J. Biotechnol., 1990, Vol. 14(3-4):363-375). This rejection is based upon the public availability of a printed publications. Claims 9-12 of the instant application are drawn to a method of producing L-amino acids using carbamoylase enzyme wherein N-carbamoyl or N-formyl amino acids are reacted and wherein said N-carbamoyl or N-formyl amino acids are produced by hydantoinases from corresponding hydantoins and wherein said hydantoins used are constantly reacemized by enzymatic or chemical methods. Gross et al. and Wagner et al. (see claim 8) disclose an identical method using the carbamoylase produced by *A.aurescens* and wherein N-carbamoyl or N-formyl amino acids are reacted and wherein said N-carbamoyl or N-formyl amino acids are produced by hydantoinases from corresponding hydantoins and wherein said hydantoins used are constantly

reacemized by enzymatic or chemical methods. Therefor claims 9-12 are anticipated by either Wagner et al. or Gross et al. as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gross et al. or Wagner et al. as applied to claims 9-12 above, and further in view of the common knowledge in the art regarding immobilization of enzymes. Claims 13-15 are drawn to the method of producing L-amino acids using the enzyme carbamoylase wherein said procedure is carried out in enzyme membrane reactor comprising immobilized enzyme, immobilized to EAH-sepharose.

The references of Gross et al. and Wagener et al. as they apply to claims 9-12 has already been discussed above. While the references teach the method of making L-amino acids using the enzyme, the references are silent as to the use of enzyme immobilization technique for the same. However, the technique of immobilizing the enzyme on to a solid support and use of such columns in continuous production of enzyme products are well k known in the art. The immobilization of enzyme is preferred for its main advantage of enzyme re-use in the production method which leads to lower production costs of the final products.

Therefore, with the above two references in hand and the common k knowledge in the art regarding immobilization of enzymes and its advantages, it would have been obvious to those

skilled in the art to immobilize the carbamoylase enzyme to a solid support such that the enzyme can be regenerated and reused. One of ordinary skill in the art would have been motivated to do so in order to lower production costs of the making L-amino acids. One of ordinary skill in the art would have had a reasonable expectation of success since Wagner et al. and Gross et al. already teach such a method using purified carbamoylase enzymes.

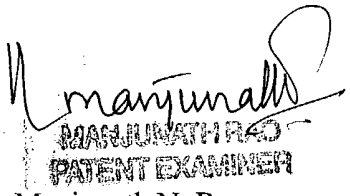
Therefore the above invention would have been *prima facie* obvious to those skilled in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
May 3, 2004